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The first-in-human study of CNTO 7160, an anti-interleukin-33 receptor monoclonal antibody, in healthy subjects and patients with asthma or atopic dermatitis

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Aims: To assess safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of CNTO 7160, an anti-interleukin-33 receptor (IL-33R) monoclonal antibody, in healthy subjects and patients with asthma or atopic dermatitis (AD).

Methods: In Part 1 of this Phase I, randomized, double-blind, placebo-controlled study, healthy subjects (n = 68) received single ascending intravenous (IV) CNTO 7160 dose (0.001 to 10 mg/kg) or placebo. In Part 2, patients with mild asthma (n = 24) or mild AD (n = 15) received 3 biweekly IV CNTO 7160 doses (3 or 10 mg/kg) or placebo.

Results: CNTO 7160 was generally well tolerated, with 1 serious adverse event of severe cellulitis reported (AD, CNTO 7160, 3 mg/kg). CNTO 7160 exhibited nonlinear PK (0.01–10 mg/kg). Mean clearance decreased with increasing dose (2.43 to 18.03 mL/d/kg). CNTO 7160 PK was similar between healthy subjects and patients with asthma or AD (3 or 10 mg/kg). Free sIL-33R suppression was rapid and dose dependent. Ex vivo inhibition of p38 phosphorylation of basophils was dose-dependent (1–10 mg/kg) and sustained inhibition (≥75%) was observed at higher doses (3 or 10 mg/kg). PK/PD modelling and simulation suggests that 1 mg/kg IV every 2 weeks provides adequate systemic drug exposure for sustained inhibition of p38 phosphorylation of basophils. Despite confirmation of target engagement, no apparent CNTO 7160 clinical activity was observed in patients (asthma or AD).

Conclusion: This first-in-human study provides PK, PD and safety data, supporting further clinical investigation of CNTO 7160 in patients with asthma and AD.

KEYWORDS

asthma, atopic dermatitis, CNTO 7160, interleukin-33 receptor, monoclonal antibody, pharmacodynamics

1 | INTRODUCTION

Interleukin IL-33 (IL-33) is a member of the IL-1 family that plays a key role in innate immunity and allergic inflammation.[1] IL-33 is produced as an alarmin by endothelial and epithelial cells in response to viral infection or allergen exposure and triggers myeloid differentiation primary response 88 (Myd88)-dependent signalling in cells expressing the IL-33 receptor (IL-33R or suppressor of tumorigenicity

The authors confirm that the Principal Investigators for this paper are Philipp Badorrek and Maarten van den Boer and that they had direct clinical responsibility forstudy participants.

2 [ST2])/IL-1 receptor accessory protein (IL-1RAcP) receptor complex.[1–5] IL-33 binds to IL-33R, which is expressed on mast cells, basophils, eosinophils, T-helper type 2 cells and group 2 innate lymphoid cells (ILC2s).[1,6–8] IL-33 signalling via IL-33R/IL-1RAcP causes downstream production of type 2 cytokines and allergic mediators, resulting in histopathological changes in the lungs and gastrointestinal tract.[2,4,9]

The IL-33 pathway has been implicated in various inflammatory diseases, including respiratory, allergic, cardiovascular, musculoskeletal, inflammatory bowel and metabolic diseases.[10] IL-33-deficient mice are protected from smoke-induced inflammatory responses to viral infection, suggesting that IL-33 is a critical mediator potentially associated with acute exacerbations of chronic obstructive pulmonary disease.[11] In addition, allergen exposure (including dust mite, ragweed and the fungal allergen *Alternaria alternata*, which are associated with asthma exacerbations) in mice leads to increased IL-33 expression, recruitment of ILC2s, and subsequent eosinophilia.[2,8,12,13] Furthermore, IL-33 expression is upregulated in human atopic dermatitis (AD) skin after allergen or microbial antigen exposure, and human skin-derived ILC2s express IL-33R and respond to IL-33 by producing type 2 cytokines, which mediate inflammation.[14,15]

Inhibition of IL-33 binding to IL-33R/IL-1RAcP may result in downregulation of both innate and adaptive immune responses, including inflammation associated with disruption to barrier function by pathogens and allergens. Therefore, antagonism of IL-33R signalling may be beneficial in treating a broad range of immune-mediated inflammatory conditions, including asthma and AD.

IL-33R has 2 main isoforms, transmembrane (IL-33R or ST2L) and soluble (sIL-33R or sST2).[10–16] The availability of IL-33 is tightly regulated by sIL-33R, which prevents interaction of IL-33 with IL-33R.[16] CNTO 7160 is a human immunoglobulin (Ig) G_2 sigma isotype monoclonal antibody without immune cell effector function[17] that binds to the extracellular domain of IL-33R and sIL-33R, blocking IL-33 binding to IL-33R and inhibiting downstream signalling and cytokine release.

The aim of this first-in-human study was to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and clinical activity of CNTO 7160 following a single ascending intravenous (IV) infusion over a wide range of doses, from 0.001 to 10.0 mg/kg in healthy subjects (Part 1), and multiple ascending IV infusions of 3 or 10 mg/kg in patients with mild asthma or AD (Part 2). The dose selection for Part 1 of this study was conservatively based a minimal anticipated biological effect level (MABEL) approach (using in vitro inhibitory activity of CNTO 7160 on the release of IL-5 in human cord blood-derived mast cells and the suppression of serum sST2 levels in cynomolgus monkeys), the predicted human PK profiles and the toxicology data in cynomolgus monkeys. The starting dose of 0.001 mg/kg in healthy human subjects (Part 1) provided predicted exposure margin of 179 805-fold and 60 726-fold relative to the maximum serum CNTO 7160 concentration (C_{max}) and area under the serum CNTO 7160 concentration *vs* time curve (AUC) over 1 week at steady state at the no-observed-adverse-effect level (NOAEL = 100 mg/kg IV) in cynomolgus monkeys, respectively. The maximum single dose of 10 mg/kg in Part 1 provided exposure margins of 18-fold and 4-fold relative to the C_{max} and AUC over 1 week at steady state at the NOAEL in cynomolgus monkeys, respectively. In Part 2, the 2 highest tolerated doses from Part 1 (3 mg/kg and 10 mg/kg) were to be evaluated following IV administration every 2 weeks in subjects with asthma and atopic dermatitis. The selected high dose of 10 mg/kg every 2 weeks was expected to yield C_{max} and AUC during a 2 week dosing interval at steady state (AUCτ) of 12-fold and 15-fold lower than the C_{max} and AUCτ over 2 weeks at the NOAEL in cynomolgus monkeys.

This paper describes the safety, PK, PD and immunogenicity results from the first-in-human study of CNTO 7160 following a single ascending IV infusion in healthy subjects or multiple ascending IV infusions in patients with mild asthma or AD.

What is already known about this subject

- The interleukin-33 (IL-33) pathway has been implicated in a range of inflammatory diseases.
- CNTO 7160, a monoclonal antibody that binds to the IL-33 receptor and blocks IL-33 signalling, may be beneficial in the management of inflammatory diseases.

What this study adds

- This first-in-human study provides pharmacokinetic, pharmacodynamic and safety data to support further clinical investigation of CNTO 7160.
- Pharmacokinetic–pharmacodynamic modelling suggests that approximately 1 mg/kg intravenously every 2 weeks is expected to provide adequate systemic drug exposures (with 90% of subjects achieving steady-state trough levels above EC_{90}) for effective inhibition of the IL-33R signalling pathway.
- CNTO 7160 was well tolerated in healthy subjects and patients with mild asthma or atopic dermatitis, and further studies in more severe patient populations are warranted.

2 | METHODS

2.1 | Participants

Participants were aged 18–55 years with a body mass index (BMI) between 19 and 30 kg/m^2 (up to 32 kg/m^2 allowed for patients with asthma) and provided written consent. Approximately 100 subjects were to be enrolled in this study: 60 healthy subjects in Part 1 and 40 patients (24 with asthma and 16 with AD) in Part 2. Part 1 included healthy subjects, eligible if they had no confounding significant illness. Part 2 included patients diagnosed with mild asthma (forced expiratory volume in the first second [FEV_1] 60–90% of predicted normal value and Asthma Control Questionnaire 6 <1.5) or mild AD (Eczema Area and Severity Index [EASI] ≥8 and ≥10% body surface area of involved skin), eligible if they had no other significant illness. Asthma patients must have been receiving an inhaled corticosteroid (≤500 μg/d fluticasone or equivalent) and/or a long-acting β-adrenoceptor agonist for at least 8 weeks prior to the screening visit.

Additional details regarding participants and study assessments are in the online supplemental information. The protocol was approved by an independent ethics committee, and the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the Good Clinical Practices and applicable regulatory requirements. The study registration identifier at ClinicalTrials.gov is NCT02345928.

2.2 | Study design

This randomized, double-blind, placebo-controlled Phase I study was conducted between August 2014 and March 2017 at 8 centres in Belgium and Germany. Part 1 was a single-ascending-dose study in healthy subjects, and Part 2 was a multiple-ascending-dose study in patients with mild asthma or AD. Both parts included a screening period of up to 4 weeks, after which participants were randomized at a 3:1 ratio (CNTO 7160:placebo), conducted by an unblinded site staff member, according to a computer-generated randomization schedule balanced by randomly permuted blocks. Participants, investigators, and sponsor study staff were blinded to treatment allocation through study completion.

2.3 | Study medication and administration

CNTO 7160 was administered by IV infusion over 30 minutes in both study parts. In Part 1, healthy subjects were randomized to receive a single-ascending dose of CNTO 7160 (0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3 or 10 mg/kg) or placebo and followed through Day 113 (Week 17). In Part 2, patients with mild asthma or AD were randomized to receive CNTO 7160 IV (3 or 10 mg/kg) or placebo biweekly (Days 1, 15 and 29) and followed through Day 141 (Week 21). The 10 mg/kg dose group included more patients with asthma than with AD (12 *vs* 5) to enhance the probability of assessing the PD response and clinical activity at this dose.

2.4 | Safety assessments

Safety assessments included physical examinations, electrocardiograms (ECGs), Holter monitoring, cardiac telemetry, clinical laboratory tests, vital signs, concomitant medications, treatment-emergent adverse events (TEAEs) and pulmonary evaluations in patients with asthma. Because sIL-33R has been observed to be increased in patients with heart failure, atherosclerosis and myocardial infarction, troponin I and N-terminal pro-brain natriuretic peptide were monitored pre- and postdose to detect heart stress or damage.

2.5 | PK assessments

Free CNTO 7160 concentration in serum was assessed after single or multiple IV infusions of CNTO 7160 using a validated, specific and sensitive electrochemiluminescent assay on the Meso Scale Discovery platform (Meso Scale Diagnostics, Rockville, MD, USA). The PK assay used 2 anti-idiotypic antibodies raised against CNTO7160 as capture and detection reagents in a typical sandwich immunoassay format. The quantification range of the standard curve was 1.6–102.4 ng/mL. The lowest quantifiable concentration was 0.016 μg/mL with minimal required dilution of 10. Dilutional linearity was demonstrated with a spiked sample at concentration of 1.024 mg/mL of CNTO7160 into 100% pooled human serum with a maximal acceptable dilution at 1:250 000. Assay performance was demonstrated with *accuracy and precision* evaluations by testing 5 levels of quality control samples over days by multiple analysts according to current regulatory guidance. The interassay precison ranged from 6 to 9% (% coefficient of variation) and the percentage recovery ranged from 107 to 112%.

The PK parameters were calculated by noncompartmental analysis using the validated computer program Phoenix WinNonlin (v.6.2.1; St Louis, MO, USA).

2.6 | Immunogenicity assessments

The immunogenicity analyses used validated immunoassays to screen the presence of anti-drug antibodies (ADA), confirm ADA specificity and determine ADA titres. The assay sensitivity was 6.2 ng/mL in the presence of 50 μg/mL CNTO 7160 in serum samples. The interassay precision was 11.8%. Neutralizing antibodies (NAbs) in ADA-positive serum samples were assessed in patients with asthma or AD. The validated NAb assay was an immunoassay with sensitivity being 131 ng/mL in 100% human serum and interassay precision being 10%. The drug tolerance for the NAb assay was 1.64 μg/mL.

2.7 | Target engagement assessments

CNTO 7160 binds to the extracellular domain of IL-33R and sIL 33R to form complexes. Interleukin-33 receptor (IL-33R), the target for CNTO 7160, conforms to the IUPHAR/BPS Guide to PHARMACOLOGY nomenclature classification.[18]

Free sIL-33R/sST2 concentration in serum (free from CNTO 7160) was assessed using a validated, specific and sensitive electrochemiluminescent assay (Meso Scale Discovery) utilizing IL-33 as a competing capture reagent and a noncompeting anti-IL-33R antibody for detection. The lowest quantifiable concentration was 0.2 ng/mL. The highest quantifiable concentration was 51.2 ng/mL. The assay demonstrated acceptable performance including accuracy and precision (% measurement error ranged from 11.7 to 20.28%). All samples were tested with no sample dilution; therefore, dilutional linearity was not assessed.

Total sIL-33R/sST2 concentration in serum (free from and bound to CNTO 7160) was assessed using a validated, specific and sensitive electrochemiluminescent assay utilizing 2 noncompeting anti-IL-33R antibodies for capture and detection. The lowest quantifiable concentration was 10.96 ng/mL. The highest quantifiable concentration was 0.2 mg/mL. The assay demonstrated acceptable performance including accuracy and precision (% measurement error ranged from 10.18 to 25.89%), and dilutional linearity from the minimum required sample dilution of 1/8 to the maximum allowable dilution of 1/200 among all parameters tested.

2.8 | PK/PD modelling

IL-33-induced basophil p38 MAPK phosphorylation was performed by ex vivo stimulation of heparinized blood with 10 ng/mL recombinant *mature* IL-33 for 10 minutes at 37°C using the Smart Tube System (Smart Tube Inc., San Carlos, CA, USA). Following stimulation, samples were fixed, frozen at –80°C and stored for analysis. Basophil p38 phosphorylation was assessed by flow cytometry (FlowMetric, Doylestown, PA, USA). Additional information on the PD assessments is provided in supplemental materials.

The relationship between serum CNTO7160 concentration (C) and the inhibition of ex vivo IL-33-induced basophil p38 phosphorylation (E) was evaluated using an E_{max} model:

$$E = E_{\max} \times C/(C + EC_{50})$$

where E_{max} is the maximum inhibition (%) and EC_{50} is the CNTO7160 concentration required to reach 50% of the maximum inhibition. Simulations were performed to assess the CNTO7160 dosing regimen to achieve a steady-state serum concentration required for ≥90% inhibition of p38 phosphorylation.

2.9 | Clinical assessments

Clinical assessment in patients with asthma included evaluation of percent-predicted forced vital capacity, percent-predicted FEV_1 and FEV_1/forced vital capacity ratio in patients who did not take a short-acting β agonist within 6 hours and did not take a long-acting β2 agonist within 12 hours of spirometry assessments. Clinical assessment in patients with AD included evaluation of AD severity using the SCORing Atopic Dermatitis (SCORAD) index (incorporates objective physician estimates of extent and severity of disease[19]), EASI score[20] and subjective patient assessment of itch and sleep loss.

2.10 | Statistical analysis

Data were summarized using descriptive statistics; no formal hypothesis testing was conducted.

2.11 | Sample size determination

No formal sample size and power calculations were performed. The number of subjects chosen for this study was to provide a preliminary safety and PK assessment of CNTO 7160 and allow for a qualitative assessment of the immunogenicity of CNTO 7160. Approximately 100 subjects were to be enrolled in this study. In Part 1 approximately 60 healthy subjects were to be enrolled in 9 cohorts (0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3 and 10 mg/kg). Four subjects were to be enrolled in each of the first 3 cohorts and 8 subjects in each of the remaining 6 cohorts. In Part 2, approximately 40 subjects (n = 24 asthma subjects, and n = 16 atopic dermatitis subjects in the 3 and 10 mg/kg cohorts) were to be enrolled. The 10 mg/kg asthmatic cohort was to include 16 subjects to better characterize the biomarker response at this dose.

2.12 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | Study population

A total of 68 healthy subjects were randomized in Part 1; 51 to CNTO 7160 dose groups and 17 to placebo. Three subjects each received CNTO 7160 0.001, 0.003 and 0.01 mg/kg; 6 subjects each received CNTO 7160 0.03, 0.1, 0.3, 1 and 3 mg/kg; and 12 subjects received CNTO 7160 10 mg/kg (6 in a planned dose group and 6 in a repeat dose group to further evaluate safety due to an episode of sinus tachycardia in the planned dose group. One subject in the CNTO 7160 0.1 mg/kg dose group discontinued the study at Day 22 for personal reasons. Baseline demographics were similar between CNTO 7160- and placebo-treated subjects and among the CNTO 7160 dose groups (Table S1). Overall, 82.4% of subjects were male, 97.1% were white, mean age was 40.2 years (standard deviation [SD], 11.4), and mean BMI was 24.9 (SD, 2.7) kg/m^2.

Thirty-nine patients with mild asthma or AD (24 asthma and 15 AD) were randomized in Part 2. Six patients with asthma and 6 patients with AD were randomized to receive CNTO 7160 3 mg/kg, 12 with asthma and 5 with AD were randomized to receive CNTO 7160 10 mg/kg, and 6 with asthma and 4 with AD were randomized to receive placebo. One patient with asthma in the CNTO 7160 10 mg/kg group discontinued the study at Day 14 due to withdrawal of consent.

Baseline demographics in Part 2 were generally comparable between CNTO 7160- and placebo-treated patients (Table S2). Overall, most patients were male (70.8% in patients with asthma, 73.3% in patients with AD) and white (100% in both patient groups). Mean age was 38.3 (SD, 10.9) years in patients with asthma and 31.7 (SD, 9.2) years in patients with AD. Mean BMI was 25.4 (SD, 3.5) kg/m^2 in patients with asthma and 23.8 (SD, 2.8) kg/m^2 in patients with AD.

Disease symptoms were mild at baseline in both disease populations (Table S2). In patients with asthma, the prebronchodilator total mean percent-predicted FEV_1 was 74.02%, mean methacholine PC20 was 1.79 mg/mL, mean Asthma Control Questionnaire 6 overall score was 0.47, and all patients were on inhaled corticosteroids (≤500 μg/d fluticasone propionate or equivalent) ± long-acting β2 agonist. In patients with AD, total mean EASI score was 20.0, mean SCORAD was 49.2, and no patients had used topical corticosteroids or topical calcineurin inhibitors within 4 weeks prior to Day 1.

3.2 | Safety and tolerability

At least 1 TEAE occurred in 42 of 51 (82.4%) healthy subjects who received a single CNTO 7160 dose and 11 of 17 (64.7%) subjects who received placebo (Table S3). TEAEs that occurred in 5% or more healthy subjects and in more CNTO 7160-treated subjects than placebo-treated subjects were gastroenteritis (7.8 *vs* 5.9%), rhinitis (7.8 *vs* 0%), sinus tachycardia (7.8 *vs* 5.9%), diarrhoea (5.9 *vs* 0%), fatigue (5.9 *vs* 0%), and myalgia (5.9 *vs* 0%). The frequency of these TEAEs in CNTO 7160-treated subjects was not related to dose of CNTO7160. The number of subjects in the MedDRA SOCs with these TEAEs were comparable between CNTO7160 and placebo: infections and infestations (19 of 51 subjects [37.3%] in the combined CNTO 7160 group compared with 6 of 17 subjects [35.3%] in the placebo group); gastrointestinal disorders (9 of 51 subjects [17.6%] in the combined CNTO 7160 group compared with 2 of 17 subjects [11.8%] in the placebo group); and general disorders and administration site conditions (8 of 51 subjects [15.7%] in the combined CNTO 7160 group compared with 1 of 17 subjects [5.9%] in the placebo group). All TEAEs in healthy subjects were mild to moderate in intensity and were dose independent. No deaths or discontinuations due to TEAEs occurred in healthy subjects.

At least 1 TEAE occurred in 26 of 29 (89.7%) patients with asthma or AD treated with CNTO 7160 and 9 of 10 (90.0%) patients treated with placebo (Table S4). TEAEs that occurred in 5% or more patients with asthma or AD and in more CNTO 7160-treated patients than placebo-treated patients were nasopharyngitis (31.0 *vs* 30.0%), contact dermatitis (24.1 *vs* 10.0%), nausea (10.3 *vs* 0%), vomiting (10.3 *vs* 0%), back pain (10.3 *vs* 0%), and diarrhoea (6.9% *vs* 0%). All TEAEs in these patients were mild to moderate in intensity except for 1 serious event of cellulitis of severe intensity in the AD CNTO 7160 3 mg/kg dose group. No deaths or discontinuations due to TEAEs occurred in Part 2.

The last enrolled subject in the initial healthy subject CNTO 7160 10 mg/kg dose group experienced several episodes of nonserious, moderate sinus tachycardia between 1 and 9 hours postdose that were considered to be related to the study agent. To further assess safety at this dose, a repeat healthy subject CNTO 7160 10 mg/kg dose group with additional safety assessments (pre- and postdose cardiac telemetry and Holter monitoring) was added to the protocol. No sinus or other types of tachycardia were observed in the repeat dose group, and there were no significant postdose changes noted by Holter monitoring, ECG or vital signs. Subsequently, pre- and postdose cardiac telemetry and Holter monitoring were performed in Part 2.

No episodes of unexplained tachycardia were observed in Part 2. With the continuous Holter rhythm monitoring, coincidental, non-sustained ventricular tachycardia (NSVT; defined as ≥3 beats of ventricular tachycardia at a rate of >100 beats/min for a duration <30 seconds), ranging from 3 to 19 beats, was observed in 4 patients (two at 3 mg/kg, 1 at 10 mg/kg and 1 placebo). In 3 of these cases, NSVT occurred while the patient was sleeping. There were no symptoms associated with NSVT, the ventricular tachycardia was monomorphic and not suggestive of Torsades, and there was no evidence of corrected QT interval prolongation after study agent administration in these patients. There were no significant abnormal findings for troponin I or N-terminal pro-brain natriuretic peptide during the study. All abnormal values were transient and only slightly higher than the upper limit reference range.

3.3 | PK

Mean CNTO 7160 concentrations in serum peaked at the first sampling timepoint (approximately 1 hour relative to the start of IV infusion), then declined in an exponential manner following a single CNTO 7160 IV infusion of at least 30 minutes in healthy subjects (Figure 1A). The mean maximum observed serum CNTO 7160 concentration (C_{max}) increased in an approximately dose-proportional manner across all dose groups. The mean area under the serum concentration–time curve from zero to infinity with extrapolation of the terminal phase (AUC_{inf}) appeared to increase in a more than dose-proportional manner from 0.01 to 10 mg/kg; however, AUC_{inf} appeared to increase in an approximately dose-proportional manner from 1 to 10 mg/kg. Mean total systemic drug clearance (CL) values ranged from 2.43 to 18.03 mL/d/kg, mean volume of distribution at terminal phase (V_z) ranged from 46.58 to 69.84 mL/kg, and mean terminal half-life ($t_{1/2}$) ranged from 2.67 to 20.55 days. There was a trend for CL to decrease and $t_{1/2}$ to increase with increasing CNTO 7160 dose (0.01 to 10 mg/kg) in healthy subjects (Table 2).

Mean CNTO 7160 serum concentration–time profiles were similar between patients with asthma and AD who received 3 biweekly doses of CNTO 7160 (Figure 1B). For both disease populations and dose groups, free CNTO 7160 serum concentrations decreased slowly in a biexponential manner, and similar terminal elimination phases

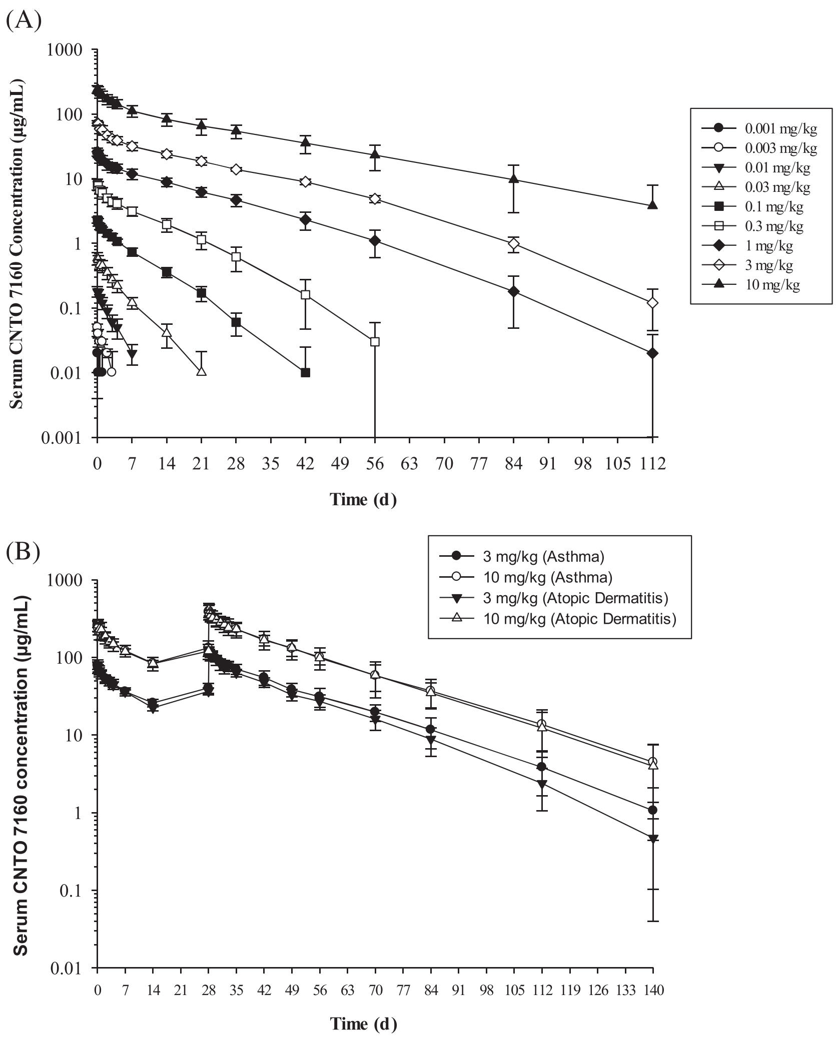

FIGURE 1 Mean (standard deviation) serum CNTO 7160 concentration–time profiles (semi-log scale) after a single CNTO 7160 IV infusion in healthy subjects (A), or biweekly CNTO 7160 IV infusions in patients with asthma or atopic dermatitis (B)

were observed after the third CNTO 7160 IV dose. Biweekly CNTO 7160 infusions resulted in approximately dose-proportional increases in exposure between 3 and 10 mg/kg. The mean accumulation ratio between the first (Day 1) and third (Day 29) infusions was between 1.70 and 1.88 for both disease populations at both doses, indicating modest accumulation up to Day 29. However, steady-state conditions had not been reached by Day 29. Following the last CNTO 7160 infusion at Day 29 in patients with asthma or AD, the mean CL values ranged from 2.86 to 3.29 mL/d/kg, mean V_z ranged from 61.6 to 75.6 mL/kg, and mean $t_{1/2}$ ranged from 13.1 to 17.6 days across both dose groups and disease populations. PK parameters in patients with asthma and AD were generally similar to those in healthy subjects (3 and 10 mg/kg) and were similar between patients with asthma and AD in both dose groups (Tables 1 and 2).

3.4 | Target engagement

Mean free sIL-33R/sST2 concentrations in serum were suppressed rapidly and in a dose-dependent manner in all healthy subjects who received a single CNTO 7160 dose (Figure S1A) and in patients with asthma or AD who received 3 biweekly CNTO 7160 doses (Figure S1B). In healthy subjects, the time to maximum suppression was 4 hours postdose across all dose groups, with >95% suppression following single CNTO 7160 IV doses of 0.1 to 10 mg/kg (Figure S1A). In patients with asthma or AD, near-maximal suppression of free sIL-33R/sST2 was achieved at 4 hours to 1 day postdose, with 98.13 and 98.45% suppression in the asthma 3 and 10 mg/kg dose groups, respectively, and 96.64 and 97.97% suppression in the AD 3 and 10 mg/kg dose groups, respectively, at 3 days postdose (Figure S1B). The time for mean free sIL-33R/sST2 serum concentrations to return to baseline increased in a dose-dependent manner in all healthy subject and asthma and AD dose groups.

Mean total sIL-33R/sST2 concentrations in serum and the time to reach maximum total sIL-33R/sST2 concentration increased in an approximately dose-dependent manner following a single CNTO 7160 dose of 0.1 to 10 mg/kg in healthy subjects (Figure S2A) and following biweekly CNTO 7160 IV administration (3 or 10 mg/kg) in patients with asthma or AD (Figure S2B). The mean maximum total sIL-33R/sST2 concentrations in serum were 76.07 and 71.78 ng/mL in the asthma 3 and 10 mg/kg dose groups, respectively, and 41.04 and 70.23 ng/mL in the AD 3 and 10 mg/kg dose groups, respectively.

TABLE 1 Mean (standard deviation) pharmacokinetic parameters after a single CNTO 7160 intravenous infusion in healthy subjects

	CNTO 7160 (mg/kg)								
	0.001	0.003	0.01	0.03	0.1	0.3	1	3	10
n	2	3	3	6	6	6	6	6	12
C_{max} (μg/mL)	0.02 (0.01)	0.04 (0.01)	0.18 (0.03)	0.59 (0.13)	2.30 (0.26)	8.20 (1.57)	26.08 (3.58)	72.92 (5.70)	245.25 (32.92)
AUC_{last} (μg·d/mL)	0.02 (–)	0.07 (0.02)	0.48 (0.11)	2.46 (0.50)	14.83 (1.59)	70.70 (16.19)	357.25 (69.28)	1067.03 (95.68)	4271.46 (1130.52)
AUC_{inf} (μg·d/mL)	NA	NA	0.58 (0.15)	2.62 (0.50)	15.45 (1.77)	71.19 (16.44)	358.12 (69.46)	1069.46 (95.55)	4415.40 (1293.30)
$t_{1/2}$ (day)	NA	NA	2.67 (0.28)	4.13 (1.18)	6.10 (0.78)	7.51 (1.15)	11.57 (1.64)	13.27 (1.58)	20.55 (5.86)
CL [a] (mL/d/kg)	NA	NA	18.03 (4.69)	11.84 (2.28)	6.55 (0.79)	4.40 (0.95)	2.89 (0.60)	2.82 (0.26)	2.43 (0.61)
V_z [a] (mL/kg)	NA	NA	69.24 (19.22)	69.84 (20.93)	57.27 (6.90)	46.58 (6.33)	47.35 (6.42)	54.09 (8.37)	67.70 (7.49)

[a] Body weight-adjusted value.

AUC_{inf}, area under the serum concentration–time curve from time 0 to infinity with extrapolation of the terminal phase; AUC_{last}, area under the serum concentration–time curve from time zero to the time corresponding to the last quantifiable serum concentration; CL, total systemic drug clearance after intravenous administration; C_{max}, maximum observed serum concentration; NA, not available; $t_{1/2}$, terminal half-life; V_z, volume of distribution at terminal phase.

The time to reach maximum total sIL-33R/sST2 serum concentration was 33 and 35 days postdose in the asthma 3 and 10 mg/kg dose groups, respectively, and 33 and 84 days in the AD 3 and 10 mg/kg dose groups, respectively.

3.5 | PK/PD modelling

Assessment of ex vivo IL-33-stimulated p38 phosphorylation in basophils demonstrated a sustained, dose-dependent inhibition of p38 phosphorylation in healthy subjects who received single CNTO 7160 doses of 1, 3 or 10 mg/kg (Figure 2A) and in patients with asthma or AD who received biweekly CNTO 7160 doses of 3 or 10 mg/kg (Figure 2B). At a dose level of 3 or 10 mg/kg, ≥75% inhibition of p38 phosphorylation was observed for up to 15 days postdose in healthy subjects and up to 30 days postdose in patients with asthma or AD. It should be noted that Figure 2 presents the raw data of percent p38 phosphorylation of basophils at different timepoints for each dose group instead of percent of baseline (pre-dose).

IL-33-induced p38 phosphorylation in basophils was considered the most relevant PD marker for PK/PD modelling and dose selection for further development since this is a functional PD measure. A nonlinear maximum percent inhibition (E_{max}) model was adequate to describe the relationship between serum CNTO7160 concentrations and the percent inhibition from baseline (pre-dose) of ex vivo IL-33-stimulated p38 phosphorylation in basophils (Figure 3A). The E_{max} was estimated to be 95.2%, indicating that blocking IL-33R with CNTO7160 administration is capable of completely inhibiting p38 phosphorylation. The EC_{50} was estimated to be 1.54 μg/mL and an EC_{90} of ~14 μg/mL was derived. There was no apparent difference in this relationship in healthy subjects and subjects with asthma and AD. To achieve steady-state serum CNTO 7160 concentrations above EC_{90}, a dose regimen of 1 mg/kg CNTO 7160 IV every 2 weeks is needed, which is expected to result in steady-state trough concentration levels above EC_{90} in approximately 90% of subjects (Figure 3B).

3.6 | Immunogenicity

Three of 51 (5.9%) healthy subjects treated with a single CNTO 7160 dose (one each in the 0.03, 1 and 3 mg/kg treatment groups) were positive for ADA against CNTO 7160 at 1 or more time points. One placebo-treated healthy subject was positive for CNTO 7160 antibodies on Days 29 and 85, suggesting that human serum from certain patients may show reactivity in the ADA assay. In general, the serum CNTO 7160 concentration–time profiles in the healthy subjects who tested positive for antibodies to CNTO 7160 were similar to those healthy subjects who tested negative for antibodies to CNTO 7160 within the same dose groups.

Overall, 3 of 29 CNTO 7160-treated patients with asthma or AD were positive for CNTO 7160 antibodies at 1 or more time points (1 of 18 [5.6%] patients in the asthma group and 2 of 11 [18.2%] patients in the AD group). Of 3 ADA-positive patients, 1 (33.3%;

TABLE 2 Mean (standard deviation) pharmacokinetic parameters at day 29 following the last of 3 biweekly intravenous infusions of CNTO 7160 in patients with asthma or atopic dermatitis

	CNTO 7160			
	3 mg/kg		10 mg/kg	
	Asthma	Atopic dermatitis	Asthma	Atopic dermatitis
n	6	5	10	5
C_{max} (μg/mL)	122 (12.0)	123 (12.0)	410 (90.7)	411 (64.9)
AUC_{τ} (μg·d/mL)	1063 (123)	924 (114)	3,461 (836)	3362 (539)
CL [a] (mL/d/kg)	2.86 (0.36)	3.29 (0.38)	3.07 (0.82)	3.04 (0.50)
V_z [a] (mL/kg)	64.3 (7.62)	61.6 (14.5)	75.5 (15.5)	75.6 (18.5)
$t_{1/2}$ (d)	15.8 (3.0)	13.1 (3.1)	17.6 (3.2)	17.3 (3.5)
R	1.88 (0.10)	1.70 (0.25)	1.82 (0.23)	1.78 (0.16)

[a]Body weight-adjusted value.

AUC_{τ}, area under the serum concentration–time curve during a dosing interval; CL, total systemic drug clearance after intravenous administration; C_{max}, maximum observed serum concentration; R, accumulation ratio calculated from AUC_{τ} after the last dose and $AUC_{0\text{-}14day}$ after the first dose; $t_{1/2}$, terminal half-life; V_z, volume of distribution at terminal phase.

AD3 mg/kg dose group) also tested positive for NAbs at Day 141 after treatment with CNTO 7160. No impact of ADAs on CNTO 7160 PK was observed in these patients.

3.7 | Clinical assessments

In patients with mild asthma or AD, changes in pulmonary or dermatological assessments, respectively, were comparable between CNTO 7160-treated and placebo-treated patients. In patients with mild asthma, the mean changes from baseline in percent-predicted FEV_1 were comparable between CNTO 7160 dose groups and between CNTO 7160-treated and placebo-treated patients from Day 2 through the end of study visit (Figure 4). Similarly, in patients with mild AD, the mean changes from baseline in SCORAD index scores (Figure 5) and EASI scores (data not shown) were comparable between CNTO 7160 dose groups and among CNTO 7160-treated and placebo-treated patients from Day 2 through the end of study visit.

4 | DISCUSSION

In this first-in-human study, CNTO 7160, a first-in-class, human monoclonal antibody against IL-33R, was well tolerated following single IV infusions from 0.001 to 10 mg/kg in healthy subjects and 3 biweekly IV infusions of 3 or 10 mg/kg in patients with mild asthma or AD.

The dose selection for this study was based on a MABEL approach using the inhibitory acbetweetivity of CNTO 7160 on release of IL-5 in human cord blood-derived mast cells and the suppression of serum sST2 levels in cynomolgus monkeys. CNTO 7160 dose-dependently inhibited IL 33-induced IL-5 release by human cord blood mast cells (CBMCs) with a mean concentration for 50% inhibition of 0.595 μg/mL. The minimal inhibitory effect of CNTO 7160 in CBMCs was expected to occur at a concentration for 10% inhibition of 0.0295 μg/mL (Janssen data, not shown). Based on the predicted human serum concentrations of CNTO 7160, a dose of 0.001 mg/kg would result in a C_{max} of 0.03 μg/mL, which was considerably lower than the observed mean 50% inhibition values in CBMCs and other in vitro activity assays.

The PK/PD results following single IV administration of CNTO 7160 in healthy subjects from Part 1 and multiple doses in patients with asthma or AD were used to guide selection of potential dosing regimens for future clinical studies in asthma, AD or other inflammatory diseases. CNTO 7160 showed dose-dependent inhibition of ex vivo whole blood IL-33 induced p38 phosphorylation of basophils in healthy subjects, and there was no apparent difference in this relationship between healthy subjects and patients with asthma or AD. An E_{max} model adequately described the relationship between serum concentrations of CNTO 7160 and the inhibition of ex vivo p38 phosphorylation in basophils. The estimated CNTO 7160 EC_{50} was 1.54 μg/mL, and EC_{90} was about 14 μg/mL. PK simulation suggests that a dosing regimen of 1 mg/kg CNTO 7160 IV every 2 weeks would maintain a steady-state trough level above 14 μg/mL in approximately 90% of subjects, which can be a useful reference for dose selection in future clinical studies.

There were no dose-dependent increases in the incidence of TEAEs in either healthy subjects or patients with mild asthma or AD, no discontinuations due to TEAEs, and no deaths. The frequency of these TEAEs in CNTO 7160-treated subjects was not related to dose of CNTO7160. The number of subjects in the MedDRA SOCs with these TEAEs were comparable between CNTO7160 and placebo. Furthermore, there were no clinically significant changes from baseline for vital signs, ECGs, Holter monitoring, physical examinations and/or laboratory parameters.

After single ascending doses, the mean C_{max} increased approximately dose proportionally across all doses. In contrast, mean AUC_{inf} increased in a more than dose-proportional manner from 0.01 to

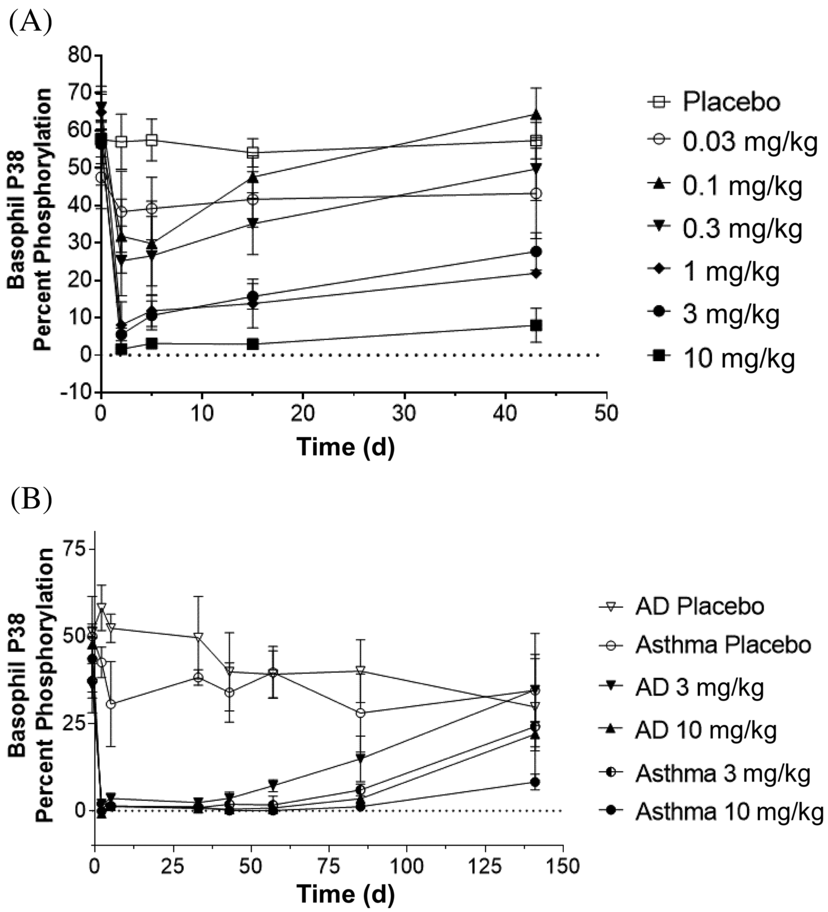

FIGURE 2 Mean (standard deviation) percent *ex-vivo* IL-33-induced p38 phosphorylation of basophils over time after a single CNTO 7160 intravenous infusion in healthy subjects (A), or biweekly CNTO 7160 intravenous infusions in patients with asthma or atopic dermatitis (B)

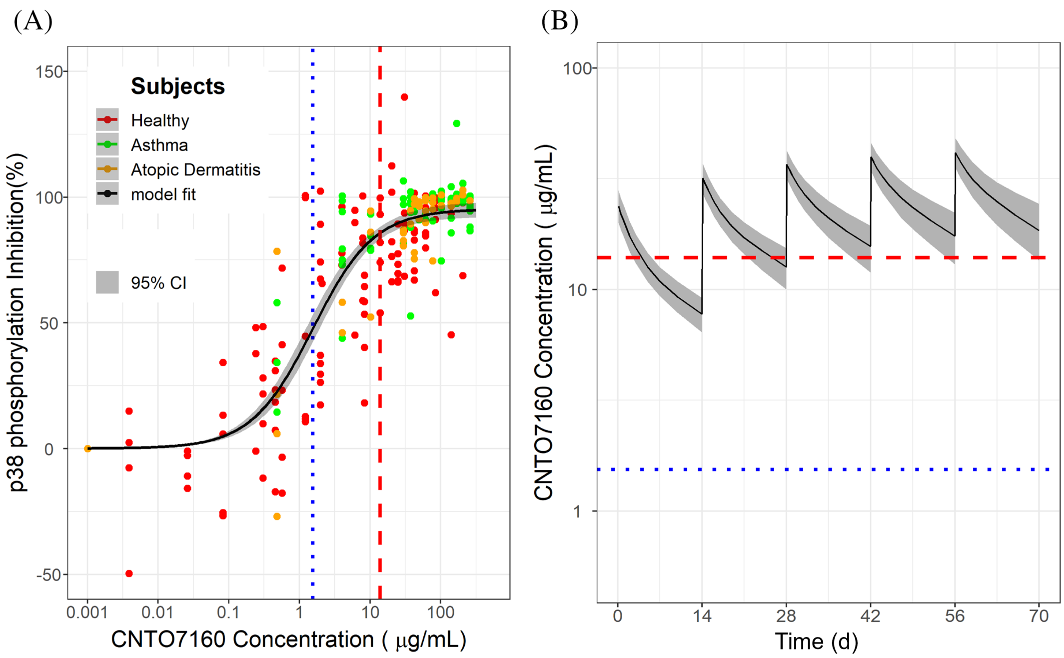

FIGURE 3 Pharmacokinetic–pharmacodynamic relationship of CNTO 7160 concentration and the percent inhibition of ex vivo interleukin-33-induced p38 phosphorylation of basophils (A), and the model-predicted CNTO7160 concentrations following intravenous administration of 1 mg/kg every 2 weeks (B). The vertical blue and red dotted lines in plot a represent EC_{50} and EC_{90} estimated from the pharmacokinetic–pharmacodynamic model, respectively. The lower and upper lines of the shaded area in B, represent the 10^{th} and 90^{th} percentile of the model-predicted CNTO 7160 concentrations, respectively, following intravenous administrations of 1 mg/kg every 2 weeks. CI, confidence interval

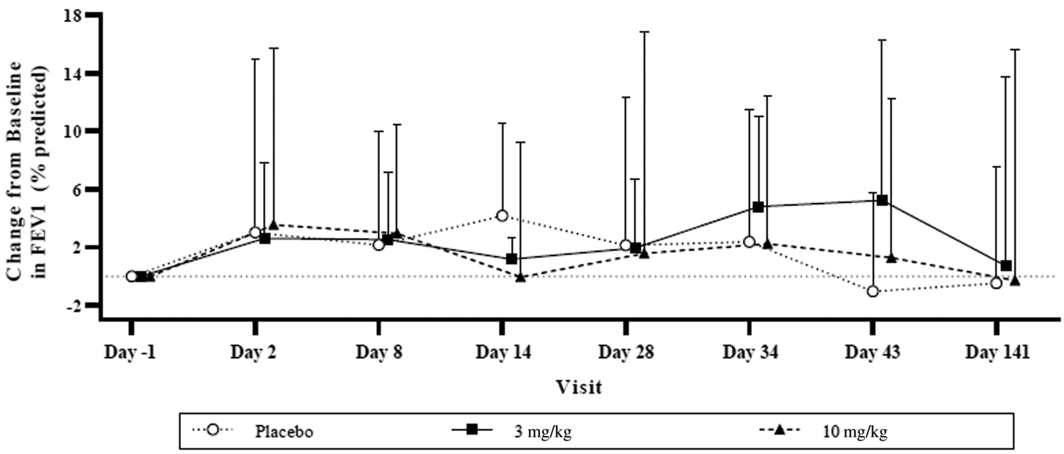

FIGURE 4 Mean (standard deviation) percent predicted forced expiratory volume in the first second (FEV1) change from baseline–time profiles after biweekly CNTO 7160 IV infusions in patients with asthma

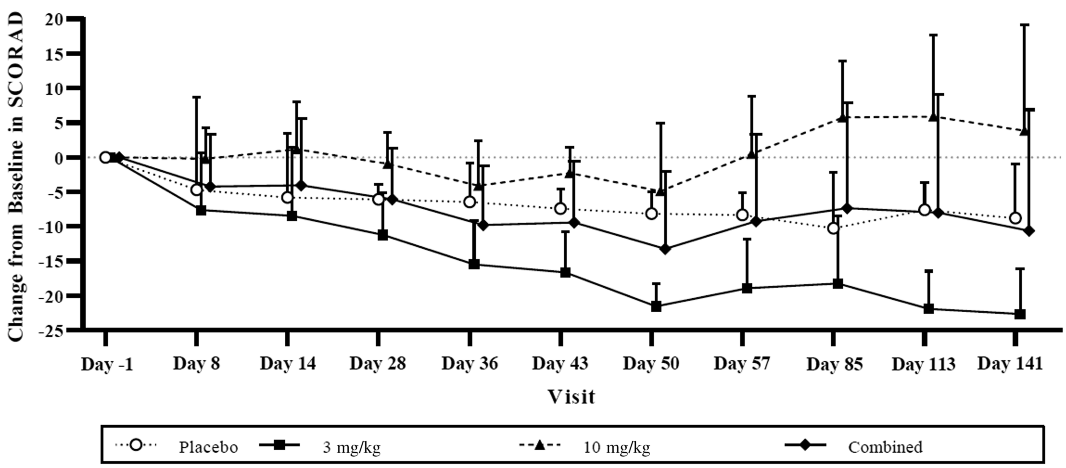

FIGURE 5 Mean (standard deviation) change from baseline in SCORing Atopic Dermatitis (SCORAD) scores after biweekly CNTO 7160 IV infusions in patients with atopic dermatitis

1 mg/kg. However, mean AUC_{inf} increased approximately dose proportionally from 1 to 10 mg/kg. Following multiple ascending doses, CNTO 7160 C_{max} and $AUC\tau$ increased approximately dose proportionally for the 3 and 10 mg/kg biweekly doses in patients with asthma or AD. The PK parameters were generally similar in healthy subjects and in patients with asthma or AD (at 3 and 10 mg/kg), suggesting that these diseases did not influence the PK of CNTO 7160. Overall, these findings indicate that CNTO 7160 exhibits nonlinear PK from 0.001 to 1 mg/kg.

Furthermore, there was a trend for CL to decrease with increasing IV doses (from 0.01 to 1 mg/kg), probably due to target-mediated drug disposition. However, mean CL values across the healthy subject CNTO 7160 1 to 10 mg/kg dose groups were similar and fell within the range of CL values for IgG-based monoclonal antibodies that are approved for treatment of asthma or atopic dermatitis such as omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab.[21,22] It is possible that the relatively constant CL of CNTO 7160 at higher doses (3 and 10 mg/kg) is due to target (IL-33R) saturation. The mean V_z values across the 0.01 to 10 mg/kg groups were similar to blood volume and comparable to those reported for human IgG monoclonal antibodies.[21,22] These findings indicate that CNTO 7160 may be distributed mostly within the vascular compartment. The mean half-life of CNTO 7160 after 3 or 10 mg/kg multiple IV doses in asthma and atopic dermatitis patients ranged from approximately 13 to 18 days, which was comparable to that of benralizumab, a humanized monoclonal antibody of the IgG_1 class which binds IL-5Ra, with a mean elimination half-life of about 7–16 days at doses of 0.03 and 3 mg/kg IV and 25–200 mg SC in asthma patients.[21,22] The PK of benralizumab was approximately dose-proportional in patients with asthma following subcutaneous administration over a dose range of 20–200 mg. In contrast, dupilumab, a humanized anti-IL-4 receptor-α monoclonal antibody, exhibited nonlinear target-mediated PK similar to CNTO 7160, with exposures increasing in a greater than dose-proportional manner, and its elimination half-life depeding on the dose level.[21,22]

Overall, the incidence of CNTO 7160-induced ADAs was low in this first-in-human study. The low CNTO 7160-induced ADAs was consistent with that of other monoclonal antibodies (including omalizumab, mepolizumab, benralizumab and reslizumab) approved for the treatment of asthma.[23] Additionally, there was no apparent impact of ADAs on the clearance of CNTO 7160 in ADA-positive patients after single or multiple CNTO 7160 IV infusions. However, it is difficult to definitively assess the impact of antibodies to CNTO 7160 on the serum CNTO 7160 concentration–time profiles in patients due to the very small number of CNTO 7160 ADA-positive patients.

The dose-dependent suppression of free sIL-33R/sST2, increase in total sIL-33R/sST2, and inhibition of IL-33-induced p38 phosphorylation in healthy subjects and patients with asthma or AD demonstrate a prolonged effect of CNTO 7160 on IL-33R/ST2 signal suppression. In patients with asthma, the evaluated CNTO 7160 dosing regimens delivered saturating drug concentrations, which explains why no dose dependency in total sST2 was observed in these patients.

Despite the confirmation of target engagement demonstrated by inhibition of IL-33R activity, no significant differences in either IgE or CCL-17 levels were observed over time between placebo-treated and CNTO 7160-treated healthy subjects, and there was no apparent clinical activity of CNTO 7160 in patients with mild asthma or AD for any parameter measured. However, it is difficult to make definitive conclusions due to the mild disease activity of these patients at baseline, the short duration of treatment and the small sample size. The pattern of IL-33R suppression and the inhibition of basophil MAPK p38 phosphorylation suggest that CNTO 7160 may have promise in treating inflammatory diseases such as asthma and AD. In AD, there is emerging evidence that IL-18 may be critical in maintaining IL-33-independent activation of ILC2s during skin inflammation.[24] Therefore, inhibition of IL-33 alone may not be optimal for the treatment of AD.

The findings from this study provide PK, PD and safety information to support further investigation of CNTO 7160 in the management of patients with asthma, AD or other inflammatory diseases.

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CONTRIBUTORS

I.N., B.F., D.R., K.D. and Z.X. designed, analyzed and reported the research; Z.Y conducted PK/PD modeling analysis; P.B., F.B., D.F., and T.-Y. Y. performed bio-analytical analyses; C.S., M.B. and P. Badorrek. contributed to the clinical conduct of the study. All authors drafted, revised and approved the manuscript.

DATA AVAILABILITY STATEMENT

The authors are currently unable to share the data used for the generation of this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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